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Editor's comment: Transcranial magnetic stimulation (TMS) has been investigated for the diagnosis or treatment of an increasing number of neurological disorders, including Parkinson's disease (PD). Although it has not yet become a staple in the Parkinsonologist's armamentarium, it is on the verge of making the leap from the laboratory to the clinic. Because of this trajectory, it is clearly important that those involved in the investigation or treatment of PD become familiar not only with the possible applications of TMS, but with its potential complications as well. In this article, VonLoh and colleagues provide a comprehensive review of the safety profile resulting from the worldwide experience with the various TMS modalities used in PD. This timely and extensive review should prove to be of immense value to PD investigators and clinicians in an era of rapidly more frequent utilization of this promising technology.

Robert L. Rodnitzky, Associate Editor Department of Neurology University of Iowa Hospital 200 Hawkins Drive Iowa City, IA 52242, USA
E-mail: robert-rodnitzky@uiowa.edu

Review

Safety of transcranial magnetic stimulation in Parkinson's disease: A review of the literature

Matthew VonLoh [a], Robert Chen [b], Benzi Kluger [a,*]

[a] Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA
[b] Department of Medicine, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) has been used in both physiological studies and, more recently, the therapy of Parkinson's Disease (PD). Prior TMS studies in healthy subjects and other patient populations demonstrate a slight risk of seizures and other adverse events. Our goal was to estimate these risks and document other safety concerns specific to PD patients.
Methods: We performed an English-Language literature search through PudMed to review all TMS studies involving PD patients. We documented any seizures or other adverse events associated with these studies. Crude risks were calculated per subject and per session of TMS.
Results: We identified 84 single pulse (spTMS) and/or paired-pulse (ppTMS) TMS studies involving 1091 patients and 77 repetitive TMS (rTMS) studies involving 1137 patients. Risk of adverse events was low in all protocols. spTMS and ppTMS risk per patient for any adverse event was 0.0018 (95% CI: 0.0002–0.0066) per patient and no seizures were encountered. Risk of an adverse event from rTMS was 0.040 (95% CI: 0.029–0.053) per patient and no seizures were reported. Other adverse events included transient headaches, scalp pain, tinnitus, nausea, increase in pre-existing pain, and muscle jerks. Transient worsening of Parkinsonian symptoms was noted in one study involving rTMS of the supplementary motor area (SMA).
Conclusion: We conclude that current TMS and rTMS protocols do not pose significant risks to PD patients. We would recommend that TMS users in this population follow the most recent safety guidelines but do not warrant additional precautions.

1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique for cortical stimulation that uses electromagnetic induction to generate a strong fluctuating magnetic field which induces intracranial currents [1]. Single pulse (spTMS) and paired-pulse TMS (ppTMS) studies have been shown to be safe and effective in studying a variety of measures of motor cortex excitability including resting

* Corresponding author. Department of Neurology, University of Colorado School of Medicine, Mail Stop B185, 12631 East 17th Avenue, Aurora, CO 80045, USA. Tel.: +1 303 724 2194.
E-mail addresses: benzi.kluger@ucdenver.edu, angela.roslawski@ucdenver.edu (B. Kluger).

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motor threshold, motor evoked potential amplitude, recruitment curves, cortical silent period, short interval intracortical inhibition, long interval intracortical inhibition and intracranial facilitation [2]. Studies of Parkinson's Disease (PD) patients using these techniques have demonstrated that PD increases net cortical excitability and that effective therapeutic interventions including medications and surgery may reduce this excitability [3]. Repetitive TMS (rTMS) applies repeated TMS pulses at set frequencies or patterns to induce changes in cortical excitability which last longer than the period of stimulus administration [4]. These alterations have generally been observed as a decrease in cortical excitability with low-frequency stimulation ($\leq$1 Hz) and an increase in cortical excitability with high frequency rTMS ($\geq$5 Hz) [5]. Patterned rTMS protocols such as theta-burst stimulation (TBS) and repetitive paired-pulse stimulation utilize more complex trains of intermittent bursts and may induce even more durable alterations in cortical excitability [6].

rTMS has been investigated as a potential therapy for numerous conditions, including depression, epilepsy, migraine, and PD [7–9]. In PD, rTMS has been studied as an intervention to improve both motor symptoms, including rigidity and bradykinesia, motor complications of therapy (e.g. dyskinesias) and non-motor symptoms, including depression and speech [10]. In general, benefits when present have been of small to moderate magnitude and short-lived. However, given the potential for clinical benefit and limitations of medical options there is a need for further studies to further develop rTMS as a therapeutic intervention and to better define the longevity, efficacy, and benefit of rTMS [11].

The use of TMS in both healthy and clinical populations has been associated with several adverse events of varying severity. The most common are transient headaches and scalp discomfort. Scalp pain and headaches are thought to be due to activation of scalp pericranial muscles [2,12]. However, more severe adverse effects may include mood changes (induction of mania), scalp burns from electrodes, and induction of seizures [2]. Seizures during TMS are thought to be a result of cortical pyramidal cell activation, spread of excitation to neighboring neurons, and overwhelming of inhibitory mechanisms [13]. Although reviews detailing the safety of TMS use exist for depression, epilepsy, and migraine, no such review exists for TMS use in PD [8,14,15]. Although PD is not associated with an increased risk of seizures, other neurophysiological changes may confer unique risks of TMS in the PD population including changes in cortical excitability and reductions in motor cortex inhibition [16]. Therefore, the purpose of this article is to provide a safety profile of TMS in PD for researchers and clinicians by reviewing the literature for any adverse events associated with TMS on PD patients.

2. Methods

2.1. Literature review

A literature search for English-language studies on TMS use in PD was conducted through PudMed. Review articles were excluded. The searches used included the following key words: *transcranial magnetic stimulation, TMS, rTMS, Parkinson*, *Parkinson's disease*, *silent period, Deep Brain Stimulation* and *theta burst*. All applicable articles were reviewed for patient demographics (gender, age, medication status), TMS protocol used (TMS modality, method of localization, number of stimuli, stimuli intensity, coil type, and coil position) and adverse events reported. The review was conducted between 1992 and December 2011.

2.2. Statistical analysis

We computed the proportion estimate of crude risk and 95% confidence intervals of seizures and other adverse events separately. We also separated single pulse and rTMS studies. Risks were calculated as per-person risk and per TMS session. Confidence intervals were calculated utilizing the Clopper-Pearson method in R software version 2.14.1. Fisher's exact test was used to compare crude risks between groups.

3. Results

3.1. Single and paired-pulse TMS

We identified 84 studies utilizing single or paired-pulse techniques in PD patients. This included 71 single-pulse protocols and 24 paired-pulse protocols including 1091 patients with PD [10,17–97] Of these studies, 2 reported adverse events and 1 reported a transient change in motor performance. No seizures were reported, thus the crude risk of seizures is 0 (95% CI: 0.0000–0.0034). The risk of any adverse event during spTMS or ppTMS is 0.0018 (95% CI: 0.0002–0.0066) per patient.

Regarding adverse events potentially related to PD, Boylan et al. described a worsening of tremor in one patient following spTMS to the motor cortex during localization [98]. As this patient was also described to have an exaggerated startle response we suspect that the change in tremor may be more related to acute stress and not a specific physiologic reaction. Cunnington et al. reported a transient increase in movement time required to complete a button pressing task in six patients following 100% maximum stimulator output (MO) spTMS of the SMA [62]. The slowing of movement only occurred when stimulation was administered early in the movement and was not found to be statistically correlated with patient age, severity of symptoms, or duration of disease. The authors hypothesized that this slowing reflected interruption of the SMA's role in movement planning and is supported by other TMS research investigating the SMA in healthy populations [99].

Regarding other adverse events, Benninger et al. reported the occurrence of ipsilateral stimulation of cranial nerve (CN) VII in one patient following spTMS administered between trains of 50 Hz rTMS of M1, however the patient experienced no cranial nerve stimulation during the 50 Hz rTMS itself suggesting that this may be a coil placement issue [100].

3.2. rTMS

rTMS refers to repetitive TMS given either continuously at a low-frequency or in intermittent trains at higher frequencies. Theta-Burst Stimulation (TBS) refers to a newer protocol where TMS stimulation is given in bursts of triplets at 50 Hz repeated in the theta range (5 Hz) either continuously (cTBS) or intermittent trains of 2 s (iTBS) [101]. We identified 77 rTMS and TBS studies involving PD patients. This included 81 separate rTMS protocols and 8 TBS protocols involving a total of 1137 patients and 11672 rTMS sessions [10,29,30,47,51,66,80,98,100,102–164]. Tables 1 and 2 summarizes the demographic characteristics of these patients, study design, TMS parameters and any adverse events for rTMS and theta-burst studies respectively. Of these studies, 14 reported the occurrence of an adverse event. There were no seizures reported. 51 adverse events were attributed to rTMS protocols. Of the 63 articles which did not report an adverse event, 33 protocols stated a lack of adverse events. The remaining 39 protocols neither stated nor denied the occurrence of any adverse events associated with rTMS or TBS. Out of 77 studies 4 reported scalp pain during treatment [98,102,118,145], 5 reported mild transient headaches [106,112,117,142,145], plus 2 studies with an unstated number of headaches [106,112,117,142,145], 2 studies reported worsening performance of a motor task [98,133], 1 TBS study reported transient (<5 min) tinnitus [102], 1 study reported nausea [112], and 1 study reported transient increase in pre-existing back pain [113].

The crude risk of seizures in PD subjects is thus 0 (95% CI: 0–0.0032) per person and 0 (95% CI: 0–0.0003) per rTMS or TBS session. The crude risk of other adverse events in PD subjects is 0.040 (95% CI: 0.029–0.053) per person and 0.0039 (95% CI: 0.0028–0.0052) per rTMS or TBS session. Comparing protocols with a single session

Table 1
rTMS data.

Author	Year	No. of subjects	On/Off medication	Age	rTMS modailty	Method of localization	rTMS frequency	No. of stimuli per session	Intensity	Coil type	Intertrain interval	Session schedule	Total number of sessions	Target	Adverse events
Gonzalez-Garcia et al. [168]	2011	17	On	57–70	High frequency	NR	25 Hz	200 (M1); 2000 (occipital lobe)	80% RMT	Fig8	NR	15 sessions over 3 months	255	M1; occipital lobe	NR
Kodama et al. [154]	2011	1	On	45	Low frequency	Maximum MEP hotspot	0.9 Hz	200 (M1 hand); 300–600 (M1 leg)	110% AMT	Fig8	NR	8 sessions over 2 months (M1 hand); 12 sessions over 3 month (M1 leg)	20	M1 hand; M1 leg	None
Rektor et al. [163]	2010	10	NR	NR	Low frequency	NR	1 Hz	600	NR	NR	NR	1 session	10	DLPFC; IFC	NR
Hartelius et al. [148]	2010	10	Off	39–67	High frequency	Maximum MEP hotspot	10 Hz	2000	90% RMT	Fig8	4 min	2 sessions over 2 consecutive days	10	M1	NR
Pal et al. [106]	2010	12	On/Off	59–70	High frequency	NR	5 Hz	600	90% RMT	Fig8	20 s	10 sessions over 10 days	120	DLPFC	Mild transient headache ($n = 2$)
Kang et al. [150]	2010	11	On/Off	48–75	High frequency	NR	25 Hz	1500	100% MT	Fig8	10 s	2 sessions	22	M1	NR
Arias et al. [138]	2010a	9	On	NR	Low frequency	NR	1 Hz	100	90% RMT	C	5 min	10 sessions over 10 days	90	Vertex	NR
Suppa et al. [160]	2010	14	On/Off	52–77	High frequency	Maximum MEP hotspot (M1); 2.5 cm anterior to the M1 hotspot (PMd)	5 Hz	1500 (PMd); 150 (M1)	90% RMT (PMd); 120% RMT (M1)	Fig8	1 min	2 sessions separated by 5 days	28	PMd; M1	None
		9	On/Off	45–63	High frequency	Maximum MEP hotspot	5 Hz	450	120% RMT	Fig8	1–2 min	1 session	9	M1	None
		5	On	54–73	High frequency	Maximum MEP hotspot	1 Hz	1500	90% AMT	Fig8	1 min	2 sessions separated by at least 5 days	10	PMd	None
Arias et al. [137]	2010b	9	On	NR	Low frequency	NR	1 Hz	100	90% RMT	C	5 min	10 sessions over 10 days	90	Vertex	NR
Borgheres et al. [169]	2010	1	NR	79	High frequency	NR	5 Hz	15	120% RMT	Fig8	NR	1 session	1	M1	NR
Balaz et al. [139]	2010	18	On	55.8 ± 6.52	Low frequency	Frameless stereotaxy	1 Hz	600	80% RMT	Fig8	NR	1 session	18	DLPFC ($n = 8$); IFC ($n = 10$)	NR
Filipovic et al. [104]	2010a	9	On	48–73	Low frequency	Maximum MEP hotspot	1 Hz	1800	90% RMT	Fig8	1 min	4 sessions over 4 days	36	M1	None
Filipovic et al. [146, 162]	2010b	10	Off	49–74	Low frequency	Maximum MEP hotspot	1 Hz	1800	90% RMT	Fig8	1 min	4 sessions over 4 days	40	M1	NR
Gruner et al. [170]	2010	15	On	56–81	Low frequency	Maximum MEP hotspot	1 Hz	900	90% RMT	Fig8	None	1 session	15	M1	None
Jacobs et al. [149]	2009	8	Off	62 ± 10	Low frequency	5 cm anterior to the TA hotspot (SMA); 2.5 cm anterior to the FDI hotspot	1 Hz	1800	80% RMT	Fig8	NR	2 sessions separated by 1 week	16	SMA; DLPFC	NR
Furukawa et al. [147]	2009	6	On	62–71	Low frequency	Maximum MEP hotspot	0.2 Hz	100	120% MT	C	NR	12 sessions over 3 months	72	M1	NR

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Table 1 (*continued*)

Author	Year	No. of subjects	On/Off medication	Age	rTMS modailty	Method of localization	rTMS frequency	No. of stimuli per session	Intensity	Coil type	Intertrain interval	Session schedule	Total number of sessions	Target	Adverse events
Narayana et al. [108]	2009	1	On	59	High frequency	Image-based robotically positioned TMS	4 Hz	400	110% MT	NR	5 s	10 sessions	10	M1	None
van Dijk et al. [161]	2009	13	On	46–75	High frequency	Maximum MEP hotspot (M1); 5 cm posterior to MEP hotspot (parietal cortex); 2.5 cm anterior to MEP hotspot (prefrontal cortex)	5 Hz	500	80% RMT	Fig8	20 s	10 sessions over 10 days	130	Parietal cortex ($n = 8$); M1 or premotor cortex ($n = 7$)	None
Baumer et al. [109]	2009	15	On/Off	63.1 ± 6.8	Low frequency	Maximum MEP hotspot	1 Hz	1200	80% AMT	Fig8	NA	4 sessions	60	PMd	NR
Benninger et al. [100]	2009	10	On	50–77	High frequency	Maximum MEP hotspot	50 Hz	1000	60% - 90% RMT	C	NR	1 session	10	M1	None
Sedlackoa et al. [110]	2009	10	Off	52–79	High frequency	Frameless stereotaxy	10 Hz	1350	100% RMT	Fig8	10 s	3 sessions separated by 10 min	30	DLPFC; occipital cortex; dorsal premotor cortex	None
Rothkegel et al. [112]	2009	22	On/Off	34–76	Low frequency	Maximum MEP hotspot	0.5 Hz	600	80% RMT	Fig8	NA	1 session	22	M1	Headache ($n = 2$), nausea ($n = 1$)
					High frequency	Maximum MEP hotspot	10 Hz	2000	80% RMT	Fig8	50 s	1 session	22	M1	
Brusa et al. [143]	2009	8	On	52–75	Low frequency	1 cm anterior to Cz	1 Hz	900	65% MO	Fig8	NA	10 sessions over 2 weeks	80	M1	NR
Cardoso et al. [142]	2008	11	Off	67 ± 8.3	High frequency	5 cm anterior to optimal stimulation of abductor pollicis brevis	5 Hz	3750	120 % MT	Fig8	NR	12 sessions over 4 weeks	132	DLPFC	Headache (equally distributed in both rTMS and rTMS sham groups
Filipovic et al. [171]	2008	5	On	48–74	Low frequency	Maximum MEP hotspot	1 Hz	1800	90% AMT	Fig8	1 min	4 sessions over 4 days	20	M1	None
Rodrigues et al. [47]	2008	6	On/Off	62–73	Low frequency	Maximum MEP hotspot	0.2 Hz	440	130% RMT	Fig8	5 s	2 sessions, 1 on and 1 off medication	12	M1	None
Hamada et al. [113]	2008	55	On	39–82	High frequency	3-cm anterior to maximum MEP hotspot for tibialis anterior	5 Hz	1000	110% AMT	Fig8	50 s	8 sessions over 8 weeks	440	SMA	Lower back pain increased ($n = 1$)
Rektorova et al. [114]	2008	6	On	67.3 ± 7.7	High frequency	Optimum activation of FDI or TA	10 Hz	1350	90% RMT	C	NR	5 sessions over 5 consecutive days	30	DLPFC	None
Fierro et al. [66]	2008	14	On/Off	48–82	High frequency	Maximum MEP hotspot	10 Hz	500	90% MT	Fig8	30 s	2 sessions	28	M1	NR
Kim et al. [152]	2008	9	Off	43–68	High frequency	NR	5 Hz	75	90% RMT	Fig8	10 s	2 sessions over 2 consecutive days	18	M1	NR
Epstein et al. [115]	2007	14	On/Off	42–78	High frequency	MEP w/ lowest threshold	10 Hz	1000	110% RMT	Custom iron core coil	25 s	20 sessions over 10 days	280	M1	None

Kormos [172]	2007	7	Off	62–79	High frequency	NR	20 Hz	2000	80% MT	NR	28 s	10 sessions over 2 weeks	70	DLPFC	None
Rektorova et al. [157]	2007	6	On	63.7 ± 7.7	High frequency	NR	10 Hz	1350	90% RMT	Fig8	NR	5 sessions over 5 days	30	MC, DLPFC	NR
Khedr et al. [151]	2007	22	Off	45–85	High frequency	NR	25 Hz	2000	100% RMT	Fig8	50 s	36 sessions over 6 days	792	M1	NR
Anninos et al. [116]	2007	30	Off	49–80	High frequency	NR	8–13 Hz	2880–4680	1–7.5 pT	C	NR	3 sessions, 1 in lab and 2 self-administered at patient's home	90	Left and right temporal regions, frontal and occipital regions, vertex	None
Loscher et al. [155]	2007	8	On	58.5 ± 5.3	High frequency	NR	5 Hz	100	MEP = 0.5–1 mV	Fig8	1 min	1 session	8	M1	NR
Del Olmo et al. [144]	2007	8	On	54–74	High frequency	5 cm anterior to maximum MEP for FDI	10 Hz	450	90% RMT	Fig8	10 s	10 sessions over 10 days	80	DLPFC	NR
Fregni et al. [135]	2006	13	On	65.2 ± 7.9	High frequency	5 cm anterior to maximum MEP for APB	15 Hz	3000	110% RMT	Fig8	10 s	10 sessions over 2 weeks	130	DLPFC	NR
Brusa et al. [141]	2006	10	Off	61 ± 8.04	Low frequency	3 cm anterior to Cz	1 Hz	900	90% RMT	Fig8	NA	2 sessions	20	SMA	None
	2006	10	On	61 ± 8.04	Low frequency	3 cm aterior to Cz	1 Hz	900	90% RMT	Fig8	NA	5 sessions over 5 days	50	SMA	None
Cincotta et al. [29]	2006	3	NR	60–82	High frequency	Maximum MEP hotspot	5 Hz	15	120% RMT	Fig8	NA	4 sessions	12	M1	NR
Morgante et al. [30]	2006	16	On/Off	50–80	Low frequency	Maximum MEP hotspot	0.1 Hz	20	MEP = 1mV	Fig8	NA	6 sessions, 3 on medication and 3 off medication	96	M1	NR
Khedr et al. [117]	2006	55	Off	30–85	High frequency	NR	10/25 Hz	2000	100% MT	Fig8	50 s	36 sessions, 6 sessions per day for 6 days	1980	Bilateral M1 for lower limbs, Bilateral M1 for the hand	Mild, transient headache in some patients
Lomarev et al. [118]	2006	18	On	63 ± 10	High frequency	NR	25 Hz	1200	100% MT	Fig8	NR	8 sessions over a 4-week period	144	Left and right motor and DLPFC	Intolerable pain ($n = 1$)
Dias et al. [64]	2006	11	On	68.47 ± 4.75	High frequency	Maximum MEP hotspot	15 Hz	3000	110% MT	Fig8	10 s	10 sessions over 2 weeks	110	DLPFC	None
	2006	8	On	61.31 ± 8.46	High frequency	Maximum MEP hotspot	5 Hz	2250	90% MT	Fig8	5 s	1 session	8	M1	None
Strafella et al. [119]	2005	7	Off	40–66	High frequency	MEP w/ lowest threshold	10 Hz	600	90% RMT	C	10 s	2 sessions over 2 days	14	M1	NR
Boggio et al. [120]	2005	13	Off	NR	High frequency	Maximum MEP hotspot	15 Hz	3000	110% MT	Fig8	NR	10 sessions over 2 weeks	130	Left DLPFC	None
Koch et al. [153]	2005	8	Off	48–73	Low frequency	3 cm anterior to Cz	1 Hz	900	90% RMT	Fig8	NA	1 session	8	SMA	NR
					High frequency	3 cm anterior to Cz	5 Hz	900	110% RMT	Fig8	40 s	1 session	8	SMA	NR
Mir et al. [80]	2005	9	On/Off	47–73	High frequency	Maximum MEP hotspot	5 Hz	1500	90% AMT	Fig8	1 min	2 sessions	18	PMd	None
Buhmann et al. [51]	2004	16	On/Off	58.4 ± 10.5	Low frequency	Maximum MEP hotspot	1 Hz	1200	80% AMT	Fig8	NA	2 sessions over 2 weeks	32	PMd	None
Lefaucheur et al. [10]	2004	12	Off	51–76	Low frequency	Maximum MEP hotspot	0.5 Hz	600	80% RMT	Fig8	NA	1 session	12	M1	None
					High frequency	Maximum MEP hotspot	10 Hz	2000	80% RMT	Fig8	50 s	1 session	12	M1	None

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Table 1 (*continued*)

Author	Year	No. of subjects	On/Off medication	Age	rTMS modailty	Method of localization	rTMS frequency	No. of stimuli per session	Intensity	Coil type	Intertrain interval	Session schedule	Total number of sessions	Target	Adverse events
Mally et al. [156]	2004	46	On	63.9 ± 9	Low frequency	NR	1 Hz	50	25% MO (MO = 2.3T)	C	NA	42 sessions over 3 years administered in 7 sessions over 7 days	1932	Vertex	None
Fregni et al. [121]	2004	21	On	50–80	High frequency	NR	15 Hz	3000	110% MT	Fig8	NR	10 sessions over 10 days	210	Left DLPFC	NR
Koch et al. [122]	2004	20	Off	61 ± 6.83	High frequency	3 cm anterior to vertex (SMA), Intersection of coil loops at F4 (DLPFC)	5 Hz	250	100% MT	Fig8	30 s	2 sessions on 2 separate days	40	SMA and right DLPFC	NR
Bornke et al. [140]	2004	12	Off	37 - 74	High frequency	NR	10 Hz	1000	90% RMT	Fig8	10 s	2 sessions over 4 days	24	M1	None
Ikeguchi et al. [123]	2003	12	On	51–78	Low frequency	F3 or F4 of the international 10–20 system	0.2 Hz	30	70% MO	C	NA	6 sessions over 2 weeks	72	Frontal (L middle frontal gyrus, R inferior frontal gyrus); Occipital (L lingual gyrus, R posterior lobe of cerebellum)	None
Khedr et al. [124]	2003	19	Off	36–70	High frequency	Maximum MEP hotspot	5 Hz	2000	120% MT	Fig8	NR	10 sessions over 10 days	190	M1 (EDB) 1000 pulses; M1 (hand) 500 pulses/ hemisphere	NR
Okabe et al. [125]	2003	85 (1/3 received sham)	On	67.2 ± 8.2	Low frequency	NR	0.2 Hz	100	110% AMT	C	NA	8 sessions over 8 weeks	680	M1 and occipital cortex	NR
Gilio et al. [126]	2002	15	On/Off (4 patients only *off*; the rest *off/on*)	46–76	High frequency	NR	5 Hz	40 (*Off/On* medication); 160 (*Off* medication only)	120% RMT	Fig8	1 min	2 sessions in 1 day	30	M1	NR
Sommer et al. [127]	2002	11	On	35–77	Low frequency	Maximum MEP hotspot	1 Hz	900	120% RMT	Fig8	NA	3 sessions over 3 days	33	M1	None
Dragasevic et al. [145]	2002	10	On	46–72	Low frequency	6 cm anterior to point of motor threshold determination	0.5 Hz	100	110% MT	C	1 min	20 sessions over 10 days	200	Prefrontal area	Light burning sensations over the scalp ($n = 4$); mild tension headache ($n = 3$)
Boylan et al. [98]	2001	10	Off	55–77	High frequency	Visible muscle twitch	10 Hz	2000	110% MT, 68–78% MT for 3 patients	Fig8	55 s	1 session	10	SMA	Scalp discomfort at 110% maximum MEP ($n = 3$); Subclinical worsening of complex and

															preparatory movement (spiral drawing) following rTMS to SMA ($n = 5$)
Shimamoto [128]	2001	9	On	53–79	Low frequency	NR	0.2 Hz	60	78% MO (700V)	C	NA	8 sessions over 8 weeks	72	Frontal area	NR
Siebner et al. [129]	2000a	10	Off	57 ± 11	High frequency	Maximum MEP hotspot	5 Hz	2250	90% RMT	Fig8	10 s	1 session	10	M1	None
Siebner et al. [130]	2000b	10	Off	41–75	High frequency	Maximum MEP hotspot	5 Hz	2250	130% RMT	Fig8	10 s	1 session	10	M1	NR
Tergau et al. [164]	1999	7	On	54–73	Low frequency	Maximum MEP hotspot	1 Hz	500	90% MT	C	NA	1 session	7	M1	NR
					High frequency	Maximum MEP hotspot	5 Hz	500	90% MT	C	30 s	1 session	7	M1	NR
					High frequency	Maximum MEP hotspot	10 Hz	500	90% MT	C	20 s	1 session	7	M1	NR
					High frequency	Maximum MEP hotspot	20 Hz	500	90% MT	C	45 s	1 session	7	M1	NR
Mally et al. [131]	1999a	49	On	NR	Low frequency	NR	1 Hz	30, 60	15–30% MO	C	NA	10 sessions over 10 days, 14 sessions over 14 days	1176	Vertex	None
Ghabra et al. [133]	1999	11	Off	48–70	High frequency	Maximum MEP hotspot	5 Hz	NR	90% RMT	Fig8	NR	2 sessions	22	M1	Muscle jerks during motor task ($n = 11$)
Mally et al. [132]	1999b	10	On	56–73	Low frequency	NR	1 Hz	30	20% MT	C	NR	20 sessions over 10 days	200	Vertex	NR
Siebner et al. [134]	1999	12	Off	41–74	High frequency	Maximum MEP hotspot	5 Hz	2250	90% RMT	Fig8	10 s	2 sessions over 2 days	24	M1	None
Sandyk [158]	1998	2	On	49, 73	High frequency	NR	5, 7 Hz	6000, 8400	7.5 pT	NR	NR	4 5 Hz and 4 7 Hz sessions over 4 days	16	NR	NR
Pascual-Leone et al. [135]	1994	6	On/Off	48–73	High frequency	Maximum MEP hotspot	5 Hz	NR	10% RMT	Fig8	NR	3 sessions	18	M1	None
Totals		1068										11,198			17 scalp pain, 12 mild transient headaches, 1 study with an unstated number of headaches, 16 worsening performance of a motor task, 1 nausea, and 1 transient increase in pre-existing back pain

Table 2
Theta burst stimulation studies.

Author	Year	Number of subjects	On/Off medication	Age	TMS parameters	Adverse events
Stephani et al. [159]	2011	8	On	62.2 ± 8.3	3 sessions at least one week apart of M1 iTBS, sham iTBS and tRNS given at 80% rMT for 10 min.	NR
Benninger et al. [102]	2011	13	On	62.1 ± 6.9	8 sessions over two consecutive weeks of iTBS over bilateral M1 and DLPFC at 80% aMT for 600 pulses per site per session and 4800 total pulses.	Transient tinnitus (<5 min, $N = 1$) and occasional local pain during stimulation
Suppa et al. [103]	2011	20	On	48–76	1 session of iTBS over M1 at 80% aMT for a total of 600 pulses.	No adverse effects
Eggers et al. [107]	2010	8	Off	60–78	One session of cTBS over m1 at 80% aMT for a total of 600 pulses.	NR
Koch et al. [111]	2009	20	On	64.2 ± 5.4	10 sessions of bilateral cerebellar cTBS at 80% aMT for 600 pulses per side per session and 12,000 total pulses.	No adverse effects
Rothkegel et al. [112]	2008	22	Both	34–76	5 sessions on 5 consecutive days over M1 including sham iTBS (600 pulses), high frequency rTMS (10 Hz for 2000 pulses at 80%rMT), low frequency rTMS (0.5 Hz at 80% rMT for 600 pulses), cTBS (600 pulses at 80% aMT) and iTBS (600 pulses at 80% aMT)	NR
Total		91				1 episode transient tinnitus; unspecified number with occasional local pain

aMT – active motor threshold; cTBS – continuous theta burst stimulation; DLPFC – dorsolateral prefrontal cortex; iTBS – intermittent theta burst stimulation; M1 – motor cortex; rMT – resting motor threshold; tRNS – Transcranial random noise stimulation.

($N = 380$) to those with multiple sessions ($N = 688$) reveals a significant increase in risk with multiple sessions (Fisher's exact test, $p < 0.001$) suggesting that risk is at least partially cumulative over sessions rather than an all or none occurrence for certain high-risk subjects.

Regarding adverse events potentially related to PD, motor symptoms were shown to worsen of selected motor tasks in patients following certain rTMS protocols ($N = 16$). Boylan et al. reported worsening of spiral drawing in five patients following 10 Hz rTMS of the SMA [98]. This finding may relate to the role of the SMA in movement preparation as demonstrated in control subjects. Ghabra et al. reported muscle jerks during 90%, RMT 5 Hz rTMS over M1 such that eleven patients could not complete a concurrent Grooved Pegboard task. This "jerking" likely reflected MEPs induced with a lowering of motor threshold when subjects activated motor cortex during the skilled motor task. Upon rTMS intensity reduction to 75–85% RMT all patients were able to complete the task. One patient in this study also noted a worsening of action tremor at the higher stimulation intensity which resolved at 75% RMT rTMS intensity and may reveal a potential interaction between motor cortex activation, whether external or internal, and action tremor.

Regarding adverse events not related to PD, the most common adverse effects reported were headache ($N = 7$) and local pain ($N = 17$). Authors gave the following descriptions of adverse events. Pal et al. reported the occurrence of mild transient headache in two patients which required neither interruption of study or medication attention following 5 Hz rTMS of M1 [106]. Rothkegel et al. reported headache in two patients following TMS of M1, though the modality which caused the side effects was not specified out of the four used (rTMS at 0.5 Hz and 10 Hz, iTBS, and cTBS) [112]. Cardoso et al. reported an unspecified number of headaches which were spread equally amongst the rTMS group and the sham rTMS group using a sham coil [142]. Khedr et al. reported the occurrence of mild transient headache following 25 Hz rTMS of M1, though an exact number of patients experiencing the event was not stated [117]. Dragasevic et al. reported mild tension headache in 3 patients following 0.5 Hz rTMS of the prefrontal area [145]. Boylan et al. reported scalp discomfort ($N = 3$) following 10 Hz rTMS of SMA [98]. Benninger et al. reported scalp pain associated with DLPFC stimulation in nine subjects following intermittent theta-burst stimulation (iTBS) of the primary motor cortex (M1) [102] [100]. Lomarev et al. reported intolerable pain located under the coil position in one patient following 25 Hz rTMS of M1 and dorsolateral prefrontal cortex, due to which the patient dropped out of the study [118]. Dragasevic et al. reported light burning sensations over the scalp in four patients following 0.5 Hz rTMS of the prefrontal area [145]. Boylan et al. reported scalp discomfort in three patients following 10 Hz rTMS of the SMA which was alleviated by reducing the stimulus intensity from 110% motor threshold (MT) to 68%–78% MT [98].

Other adverse events reported included tinnitus ($N = 1$), nausea ($N = 1$), and an increase in previously acquired lower back pain ($N = 3$). Benninger et al. reported a nonpulsatile left-sided tinnitus for a few minutes in one subject following intermittent theta-burst stimulation (iTBS) of the primary motor cortex (M1) [102]. Rothkegel et al. reported nausea in one patient following TMS of M1, though the modality which caused the side effects was not specified out of the four used (rTMS at 0.5 Hz and 10 Hz, iTBS, and cTBS) [112]. Hamada et al. reported an increased sensation of back pain which existed prior to treatment in one patient following 5 Hz rTMS of the supplementary motor area (SMA) [113].

A number of events which either did not directly result in negative outcomes for the patient or were not attributed to the rTMS procedure were also reported. Due to this, these events were not included in the risk assessments, but are included here for completeness. Beninnger et al. reported one patient with residual muscle activity and possible spread of excitation from arm to lower extremity muscles by clinical observation following 50 Hz rTMS [100]. This subject also had a slight increase in left temporal spikes monitored by electroencephalography (EEG) but had occasional bitemporal spikes at baseline and upon further questioning after the rTMS session mentioned a prior car accident with blunt head trauma and possible loss of consciousness. Epstein et al. reported the occurrence of falls ($n = 4$), a recurrence of paroxysmal atrial fibrillation ($n = 1$), and unilateral hip pain unrelated to any acute injury ($n = 1$) during a trial of 10 Hz rTMS of M1. However these events were not temporally related to the rTMS and thus not considered side effects of rTMS treatment [115]. Mally et al. reported the occurrence of dystonia in four patients which was thought to be a result of drug treatment with levodopa and extended release levodopa and not a result of 1 Hz rTMS at the vertex [131].

Table 3
TMS use in PD Patient's with STN DBS devices.

Author	Year	Number of subjects	On/Off medication	On/Off DBS	Age	TMS parameters	Adverse events
Balaz et al. [139]	2010	18	On	Off	55.8 ± 6.5	1 session of rTMS at 80% rMT at 1 Hz over either IFC or DLPFC for 600 total pulses	NR
Kuriakose et al. [19]	2010	8	On	Both	52–75	1 session of single pulse TMS over M1 delivered every 6 seconds in 3 different coil orientations (AP, PA and perpendicular) following DBS pulses for approximately 180 total pulses	NR
Rektor et al. [163][a]	2010	10	NR	Off	NR	1 session of 1 Hz rTMS for 600 pulses over either right IFC or DLPFC; Intensity NR	NR
Baumer et al. [109]	2009	15	Both	Both	60.3 ± 6.3	4 single pulse TMS sessions over M1 consisting of rMT determination and 10 pulses at 150% of rMT over motor hotspot for SP determination	NR
Narayana [108]	2009	1	NR	Off	59	10 sessions of 4 Hz rTMS over left PMd at 110% rMT delivered in 5 second trains with a 5 second intertrain interval. 20 trains were given per session for a total of 4000 pulses	No adverse effects. TMS mimicked aspects of DBS induced speech dysfunction which was the intended effect (virtual lesion)
Gaynor et al. [22]	2008	9	On	Off	50–69	1 session including 30–50 single pulses every 5 seconds over one or both M1 and left SMA at 95% and 115% rMT	NR
Fraix et al. [68]	2008	15	Off	Both	60 ± 11	1 session over M1 of single pulse (SP, rMT, aMT, CMCT) and paired – pulse (SICI, ICF) measures for approximately 180 total pulses	No adverse effects
Potter-Nerger et al. [20]	2008	10	Off	Both	58.3 ± 8.3	1 session of 95% aMT single pulses over M1 (soleus hotspot) for approximately 60 total pulses	NR
Sailer et al. [173]	2007	7	Both	Both	56.1 ± 6.3	1 session of single pulse TMS at rMT over M1 paired with median nerve stimulation to measure SAI and LAI for approximately 80 total pulses	NR
Compta et al. [61]	2006	3	Off	Off	NR	1 session of suprathreshold SP determination for approximately 10 total pulses	NR
Hidding et al. [28]	2006	8	Off	Off	43–69	1 session of RC and CMCT over M1 at 110%-150% rMT for approximately 50 total pulses.	NR
Kuhn et al. [32]	2004	5	On	Off	56.8 ± 3.0	1 session of single pulse TMS over M1 above rMT with or without acoustic stimulation. Estimated 20–50 total pulses	NR
Dauper et al. [53]	2002	8	Both	Both	59.3 ± 10.0	4 sessions of single pulse (MEP, SP) and paired-pulse (SICI, ICF) at 120% rMT for approximately 80 total pulses	No adverse events
Cunic et al. [40]	2002	9	On	Both	41–78	3 sessions of single pulse (MT, RC, SP) and paired-pulse (SICI, LICI, ICF) M1 stimulation at 100–150% rMT at rest and active contraction for estimated 360 total pulses	No adverse effects
Pierantozzi et al. [83]	2002	4 (implanted in both bilateral STN and GPI)	Both	Both	49–60	4 sessions of single pulse (rMT) and paired-pulse (SICI) at 70%-120% rMT for approximately 120 total pulses	NR
Total		122					NR

Abbreviations: aMT – active motor threshold; CMCT – central motor conduction time; DBS – Deep Brain Stimulation; ICF – intracortical facilitation; LAI – long latency afferent inhibition; M1 – primary motor cortex; MEP – motor evoked potential; NR – not reported; PMd – dorsal premotor cortex; RC – recruitment curve; rMT – resting motor threshold; rTMS – repetitive transcranial magnetic stimulation; SAI – short latency afferent inhibition; SICI – short intracortical inhibition; SMA – supplemental motor area; SP – silent period; STN – Subthalamic Nucleus; TMS – Transcranial Magnetic Stimulation.
[a] May overlap patients in Balaz study.

Sham TMS was used in both rTMS [104,106,113,125,128,139,142,144,150,162] ($N = 142$) and TBS [102,107,111,112,159] ($N = 58$) protocols. Of these sham exposures, one patient receiving sham rTMS over SMA withdrew due to perceived worsening of symptoms [113] and one study reported a similar incidence of mild headaches in their real and sham 5 Hz DLPFC rTMS groups [142]. While the number of adverse events for both real and sham rTMS are small, Fisher's exact test ($P > 0.05$) does not reveal a significant difference between crude rates of side effects and suggests that caution may be warranted when attributing side effects observed in studies to the physiological effects of rTMS.

3.3. TMS in patients with deep brain stimulators

In 1999 Kumar et al. tested TMS pulses delivered over DBS leads embedded in conduction gel and directly over stimulators to demonstrate that TMS in DBS patients did not effect DBS leads but could disrupt stimulator function if stimulated directly over the stimulator device [165]. Since that time there have been a number of studies using TMS in PD patients following deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN; see Table 3) with no adverse events reported in 122 subjects. The crude risk of any adverse event in PD STN DBS subjects is thus 0 (95% CI: 0–0.0298) per person. While only one of these studies included patients who also had globus pallidus interna (GPI) DBS [83], studies in dystonia subjects with GPI DBS would suggest that these patients would also be reasonable candidates for future DBS research [166].

4. Conclusions

TMS has been shown to be a useful technique for studying the neurophysiology of PD and shows potential in the treatment of motor and non-motor symptoms. Our review of the literature, including 2228 patients, revealed that both TMS and rTMS do not carry significant risk of adverse events in the PD population. Based on our review, we would suggest that TMS and rTMS may have similar risks to those found in the general population and that these

risks, while low, do increase over multiple sessions. We would recommend that TMS users in this population follow the most recent safety guidelines but do not warrant additional precautions. We would however recommend that rTMS studies in PD patients monitor for motor function, particularly with SMA stimulation. We would also recommend that EEG and EMG monitoring be utilized for novel stimulation paradigms, as exemplified by Benninger et al. but do not feel that this level of monitoring needs to be used routinely [100]. Finally, preliminary evidence from 122 PD patients with DBS implants similarly suggests that TMS does not carry a significant risk in this population either.

One unique issue raised in this review is the potential for worsening motor symptoms with certain spTMS and rTMS paradigms [62,98]. The Cunnington et al. spTMS study's findings of increased time to complete a movement was attributed to a disturbance of the SMA's role in motor planning due to the occurrence of the adverse event only when administered early in the movement [62]. Detrimental effects on spiral drawing and the preparatory phase of movement due to physiological disturbance of SMA has been observed in studies prior to Boylan et al., including the Cunnington et al. study on PD patients [62,167]. The Boylan et al. study suggests that rTMS may be able to make such disruptions persist beyond the initial stimulus [98]. However, Hamada et al. found that SMA stimulation resulted in improvement of motor symptoms in PD patients as measured by UPDRS scores [113]. There are several possible causes for the difference between the two study's findings. Hamada et al. used a 5 Hz stimulation frequency as compared to Boylan et al. using 10 Hz [98,113]. In addition, Hamada et al. delivered only 1000 stimuli per session, while Boylan et al. delivered 2000 stimuli [98,113]. The increase in rTMS intensity and total number of stimuli may have caused Boylan et al. to elicit a negative outcome due to excessive excitation of the SMA. Another potential difference lies in the time course of the two studies. Boylan et al. only delivered 2 sessions at least one week apart [98]. Hamada et al. however did not see improvement of motor symptoms in their patients until at least 4 consecutive weeks of rTMS treatment [113]. Thus it is possible that reduction of risk and presence of benefit in rTMS of the SMA will only be achieved by lower intensity treatment over a longer timeframe. The conflicting results between these two studies merit further investigation of rTMS stimulation of the SMA in PD patients. We therefore recommend that rTMS studies in PD patients monitor for motor fluctuations and worsening.

All other adverse events attributed to rTMS were minor and no studies reported the need for medical care in response to an event. Out of 1137 patients 17 reported scalp pain during treatment [98,102,118,145], 7 reported mild transient headaches, plus 2 studies with an unstated number of headaches [106,112,117,142,145], 1 reported transient tinnitus [102], 1 reported nausea [112], and 1 reported transient increase in pre-existing back pain [113]. Due to their low rate of occurrence, transient nature, and complete lack of need for medical intervention these adverse events can be considered of minimal risk to the patient.

A further caveat concerns other potential risks in the PD population. First, medications should be carefully screened to ensure that medications associated with a lowered seizure threshold (e.g. antipsychotics, psychostimulants, tricyclic antidepressants, buproprion) are either excluded or carefully monitored. This would include antipsychotics and certain antidepressants. Second, PD patients should be screened as other patients for associated comorbidities including cardiac disease and epilepsy. Finally, patients with vascular Parkinsonism may have an increased risk of seizure.

We conclude that established TMS protocols have a minimal risk of adverse events in the PD patient population. PD patients should still be warned of the potential risk for seizure due to rTMS in the general population as well as a small risk of transient headache and scalp pain seen in previous PD study participants. However, the use of TMS should be encouraged in the further study of the neuronal processes underlying PD as well as an alternative treatment for PD so long as it is thought to produce clinically relevant improvements in motor function.

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Relevant conflicts of interest/financial disclosures

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